Review Article

Clinical Aspects and Management of Fibromyalgia Syndrome

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Abstract

Fibromyalgia syndrome (FMS) is a chronic and debilitating musculoskeletal pain disorder of unknown aetiology with usual accompanying features of fatigue, sleep disturbances and stiffness. Its place in medical textbooks was controversial with rheumatologists holding the helm of its management for many years. Over the last decade, abnormalities have been identified at multiple levels in the peripheral, central, and sympathetic nervous systems as well as the hypothalomo-pitutary-adrenal axis stress response system. With the elucidation of these pathways of pain, FMS is known more as a central sensitivity syndrome. This led to tremendous increment in interest in both pharmacological and non-pharmacological treatment of FMS. The United States Food and Drug Administration (FDA) has also successively approved 3 drugs for the management of fibromyalgia – pregabalin, duloxetine and milnacipran. Non-pharmacological modalities showed aerobic exercise, patient education and cognitive behavioural therapy to be most effective. Overall, management of FMS requires a multi-disciplinary approach.

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Introduction

Fibromyalgia syndrome (FMS) has been referred to as a medically unexplained syndrome;[1,2] a rheumatological entity described in rheumatology textbooks and taught to all training rheumatologists,[3] and lately with newer development in research particularly in neurophysiology, as a central sensitivity syndrome.[4] Due to its lack of objective findings on physical examination, laboratory and imaging modalities, FMS was once dismissed by physicians and the public as a psychological disorder. It was thought to be a society-driven disorder, whereby expressions of the distressed patient's problems are made into a "disease", hence becoming more legitimate for equal social support and sympathy from the medical community.[5] Whether this is actual social or economic medicalisations,[6] there are real patients suffering real symptoms.

Background

FMS is a chronic musculoskeletal pain disorder of unknown aetiology, characterised by chronic widespread pain and muscle tenderness and the presence of tender points on examination. Patients experience both allodynia (pain from a normally nonpainful stimulus) and hyperalgesia (inappropriately intense pain from a normally painful stimulus). Other common accompanying features are fatigue, sleep disturbances, stiffness, paraesthesias, headaches, Raynaud's like symptoms, depression and anxiety. FMS is much more than widespread pain as it overlaps substantially with other central sensitivity syndromes such as chronic fatigue syndrome, irritable bowel syndrome, chronic pelvic pain syndrome/ primary dysmenorrhoea; temporomandibular joint pain, multiple chemical sensitivity, restless legs syndrome and interstitial cystitis. In 1990, the American College of Rheumatology (ACR) published the classification criteria of Fibromyalgia.[7] Patients who fulfilled these criteria must have firstly, pain for at least 3 months involving the upper and lower body, right and left sides, as well as axial skeleton, and secondly, pain in at least 11 of 18 tender points on digital examination. The second criterion requires these tender points to be digitally palpated with about 4 kg per unit area of force. Although the criteria provided a sensitivity of nearly 88% and specificity of 81% in distinguishing FMS, it is important to exclude other causes of chronic musculoskeletal pain.

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Systemic diseases, such as hypothyroidism, systemic lupus erythematosus (SLE) and malignancies, can mimic FMS and have to be excluded. The classification criteria initially drew considerable criticisms of over-relying on tender points,[8] referring fibromyalgia as a discrete entity rather than a cut-point along a pain-distress continuum[9] and under-emphasising on central symptoms of the syndrome,[10] has now gained wide recognition in the medical community. Presumably, one understands that like most ACR criteria for other rheumatic diseases, it is developed for research purpose and over the years, it has aided our understanding of FMS in both research and clinical settings.

History in Brief

Clinical description of fibromyalgia has been reported since mid-1800s. In 1904, Sir William Gowers created the term "fibrositis" when he was actually referring to regional pain syndrome.[11] The term "fibrositis" hence was a misnomer and no longer used as studies have shown that there were no inflammation within the connective tissues. "Fibromyalgia" was first introduced in 1976 in an editorial to the section on non-articular rheumatism in the 22nd "Rheumatism Review" of the American Rheumatism Association (currently known as ACR). Derived from both Latin (fibra – fiber) and Greek words (myo-muscle and algos –pain), it literally means "pain in the muscle and fibrous tissues".[12] Since then, the studying of fibromyalgia has gathered momentum. A Medline literature review found that the total number of medical articles dealing with fibromyalgia/FMS has increased 5-fold during this past decade,[13] with non rheumatology journals publishing substantially more articles compared to a decade ago.

Fibromyalgia Syndrome and Rheumatology

Rheumatologists tend to be ambivalent about FMS though the condition has been traditionally perceived to be an entity from the rheumatology specialty due to the presence of physical pain and body tenderness. With the development of the ACR criteria in 1990 and the World Health Organization (WHO) providing Fibromyalgia ICD code, it has been conferred a "diagnosis" status. The general perception amongst rheumatologists is that patients with FMS takes up too much time for a busy clinical practice and having little success in managing these patients, most find FMS difficult to treat. Literature also showed FMS symptom measurements, such as pain, global severity, fatigue, sleep disturbance, anxiety, depression and health status, can remain unsatisfactory despite years of therapy.[14] In the last 2 years, some even questioned whether FMS should be cared for by the rheumatologists at all as latest evidence showed FMS to be a pain syndrome centred in the nervous system.[15,16] Although there was a recent study which showed that family physicians could be trained to diagnose FMS correctly in 70% of patients,[17] there were many factors such as physician training, ethnicity and cultural biases which can affect the outcome of that study.

Historical clinical evidence showed FMS can mimic autoimmune diseases, which was why its diagnosis was a constant challenge even to the rheumatologists. FMS patients can display symptoms suggestive of SLE such as peripheral neuropathy[18] or manifest with low titre ANA levels ranging from 8.8% to 30% in FMS patients.[19] Furthermore, FMS patients often present with bodily ache and joint pain but physical examination shows no objective evidence of synovitis.[20,21] In addition, immunoglobulin depositions without complement fixations in the skin were documented in the skin of FMS patients.[22] Sicca symptoms such as dry eyes and mouth which are characteristic of Sjorgren's syndrome has been demonstrated in FMS patients.[23] Despite these mimics, a retrospective analysis with long-term follow-up of FMS patients however showed no increased probability of FMS patients developing into any connective tissue disease.[24]

Nonetheless, FMS is the second most common musculoskeletal disorder which takes up the second most amount of time in rheumatologists' offices.[25] FMS can co-exist and affect management of other rheumatic diseases. It was estimated that 20% of patients with rheumatoid arthritis and 50% of patients with SLE suffer from fibromyalgia.[26,27]

Local Perception of Fibromyalgia Syndrome

Local studies are however lacking. In 1999, a study in Singapore showed that fibromyalgia patients exist amongst our patients.[28] Looking into 101 patients randomly selected from medical clinics and using dolorimeter to confirm the tender points, 6 patients (5.99%) fulfilled the ACR criteria for fibromyalgia. These patients had mean tender point count of 14.17 as compared to 5.58 from a sample population. Eighteen patients (17.8%) had 11 or more tender points but did not satisfy the criteria of widespread pain of more than 3 months' duration.

A survey on the awareness and perceptions of FMS in Malaysia and Singapore[29] showed more than 90% of rheumatologists surveyed believed that FMS is a distinct entity, an illness rather than a disease, involving medical and psychological realms, and is confirmed by excluding other well-defined clinical diseases through a combination of clinical evaluation and screening tests.

A more recent survey (personal communication – Feng PH. Short survey on fibromyalgia. August 2009) of Singapore rheumatologists/rheumatology trainees was undertaken in 2009. Although less than half responded, those responded believe FMS exists, do see FMS patients, use the ACR criteria for diagnosis, and treat FMS patients via a multi-disciplinary methods by co-managing these patients

with pain specialists, psychiatrists, rehabilitation physicians, physiotherapists, psychologist and medical social workers. Majority are also of the opinion that they can play a role in managing FMS patients although some think that other specialists are more suited to managing FMS patients. Indeed, there were a few responders who believed that the diagnosis of FMS need not be a diagnosis of exclusion but it is imperative to exclude certain systemic diseases such as autoimmune diseases, malignancies or metabolic diseases. Literature evidence shows FMS patients underwent unnecessary operations[30] thus consumed unnecessary healthcare resources. Positive diagnosis of FMS, on the other hand, is associated with reduced healthcare utilisation and reduction in investigations.[31,32] Unfortunately, there is still no gold standard for diagnosis of fibromyalgia. The presence of ACR criteria,[7] however, has inadvertently made the diagnosis of fibromyalgia simply to be "the blessing" of the rheumatologists.

Epidemiology of FMS

FMS is a very common condition, estimated to affect 2% to 4% of the population[33,34] although local epidemiologic study is lacking. It has a prevalence of 3.4% in women versus only 0.5% in men with a female-to-male ratio of approximately 9:1. Usually diagnosed between 20 to 50 years of age, it increased with age until aged 70 after which it decreased slightly. FMS can also occur in children at prevalence rate of 1.2% and 1.4%.[35,36] The prevalence of FMS is considerably higher in rheumatology clinic at 12% to 20% of new patients seen[37,38] whereas it occurs in 5% to 6% of adult patients presenting at general medical and family practice clinics.[31]

Aetiology and Pathogenesis

It is beyond the scope of this article to discuss the various aetiologies and pathogenesis of FMS. The exact aetiology of FMS is unknown and no single factor can lead to all the symptoms of FMS. Stress and medical illness can trigger FMS. Early studies showed there was no peripheral damage or inflammation within the muscles or tissues. Focus then shifted for alternative explanations. Investigations have focused upon central pain processing systems such as disturbances in neurotransmitter and neuroendocrine regulations, reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, including substance P, and dysregulation of the hypothalamic-pituitary-adrenal axis. FMS patients experience pain differently; they have allodynia, hyperalgesia as well as lower pain threshold as compared to normal. Sleep disruption has been implicated in FMS[39,40] and over 90% of FMS patients complain of sleep problem. Fibromyalgia-like symptoms were reproduced in normal volunteers by depriving them of deep sleep. Evidence using functional brain imaging allow visualisation of structures involved in pain processing further suggest central cause of pain.[41,42] Patients with FMS are thought to develop functional changes in the central nervous system (CNS) that result in central pain sensitisation that is manifested as increased excitability of neurons, enlargement of their receptive fields, reduction in pain threshold and recruitment of novel afferent inputs. Abnormalities have been identified at various levels in the peripheral, central, and sympathetic nervous systems, as well as the hypothalamo-pitutary-adrenal axis stress-response system.[43,44]

Despite evidence that emphasises the role of sensory and CNS abnormalities for the chronic pain associated with FMS, psychosocial factors also play an important role in the development and course of FMS.[45] These include exposure to negative life events and chronic stress, increased focus on bodily symptoms and passive pain-coping mechanisms. A recent family study[46] also found that FMS coaggregates with mood disorders in families, suggesting the possibility of shared pathophysiologic factors in FMS and mood disorders.

Management of Fibromyalgia

Numerous literatures are available on the management of fibromyalgia.[47-50] Most FMS patients have been evaluated by different specialists and undergone multiple tests. The approach is to establish a correct diagnosis, to exclude differentials and to explain the implications of the diagnosis to the patients. The goals of therapy are to improve symptoms, function and emotional well-beings. Empathetic listening and acknowledgment that the patient is indeed experiencing pain would go a long way to validate the patient's illness and establish rapport for further treatment. Prior to prescribing any form of treatment, it is imperative to assess any possible causal or perpetuating factors, including attention to psychological and sociocultural factors. Concomitant treatment of any possible nociceptive pain from an apparent pathology is important, for example, treating the pain from an inflamed bursitis or degenerative spondylosis. Excessive investigations or testings if not indicated should be discouraged. Physicians are also reminded to avoid comments such as "It's all in your mind" or "I cannot find anything wrong with you". Besides management of clinically relevant symptoms such as fatigue, depression, rigidity and sleep disorders; physical and emotional stress may aggravate FMS and needs to identified and treated appropriately.[51] Evidence has shown that multi-disciplinary rehabilitation helps at least in the short term but effort needed to maintain long-term benefits.[52,53]

Pharmacological Treatment

A range of medical therapeutics, such as anti-inflammatory drugs, opioids, muscle relaxants, antidepressants, sedatives and antiepileptics, have been used to treat FMS. With

newer understanding of the neurophysiology of the FMS pointing to a central pain processing, research into drugs has intensified. This led to drugs being approved by the United States Food and Drug Adminstration (FDA). In June 2007, pregabalin became the first treatment approved by the FDA for the treatment of FMS. Currently there are 3 FDA-approved drugs for FMS. They are Pregabalin (Lyrica; Pfizer, Inc), Duloxetine (Cymbalta; Eli Lily and Company) and Milnacipran (Savella; Forest Laboratories and Cypress Bioscience). Market survey showed the most frequent drugs used for treatment of FMS is non-steroidal anti-inflammatory drugs (NSAIDS) and since FMS is largely devoid of inflammation, it is of little wonder that these treatment failed.[54]

Alpha-2-delta ligands such as gabapentin and pregabalin were used in the treatment of many pain conditions such as painful diabetic neuropathy and postherpetic neuralgia. As a $\alpha_2\delta$ calcium-channel antagonist that acts by limiting the neuronal release of excitatory neurotransmitters, it can decrease pain, decrease sleep latency and modify sleep architecture by improving slow-wave sleep. Pregabalin was approved by the FDA for fibromyalgia after demonstrating efficacy in 3 published trials.[55-57] Generally starting at lower doses, it should reach doses such as 600 mg daily. Most patients who discontinue pregabalin do so because of somnolence and dizziness especially with higher doses. However, a meta-analysis[58] showed pregabalin at 150 mg daily was generally ineffective hence higher doses (such as 300 mg, 450 mg or 600 mg) were required. Gabapentin with the same mechanism of action has also been effective in the treatment of FMS.[59]

Anti-depressants such as tricyclic anti-depressants (TCA), selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, citalopram and paroxetine as well as dual receptor inhibitors serotonin-norepinephrine reuptake inhibitors (SNRIs) have been found to be helpful in relieving symptoms of fibromyalgia. However, it was the SNRIs which provide more benefit as compared to pure serotonergic drugs. Initial trials with the first available SNRI, venlafaxine,[60] showed conflicting results in the management of FMS. In June 2008, another SNRI duloxetine was approved by the FDA for the management of FMS. Duloxetine was previously approved for the treatment of peripheral neuropathic pain, depression and generalised anxiety disorder. This new approval was based on data from 2 pivotal double-blind, fixed-dose, randomised, phase-3 clinical trials of 12 weeks' duration.[61,62] A subsequent 6-month multi-centre, randomised, double-blind placebo-controlled trial[63] showed reduction in pain severity and global assessments at 3 and 6 months, irrespective of depression status. The recommended dose of duloxetine is 60 mg once daily and no additional benefit was observed in patients receiving 120 mg once daily. Treatment should be initiated at 30 mg once daily for 1 week to allow patients to adjust to the medication before increasing to 60 mg once daily dosing. Improvement in pain can be felt as early as the first week and this benefit persisted throughout the study period. The common side effects of duloxetine were nausea, dry mouth, constipation, decreased appetite, somnolence, hyperhidrosis and agitation.

Another SNRI, milnacipran, was approved in January 2009 for the management of fibromyalgia after its efficacy was established in 2 pivotal US phase 3 trials.[64-66] Milnacipran was found to have greater efficacy than placebo for pain relief, improvement in global well-being and physical function. The recommended dose of milnacipran is 100mg or 200 mg daily. Adverse effects of milnacipran such as nausea, headache and constipation are the main reasons for discontinuation of treatment. Milnacipran is not available in Singapore at this point of time.

In practice, patients often respond to combination of pharmacological treatments, although studies of combination pharmacotherapy are still limited. A $\alpha_2\delta$ calcium-channel antagonist gabapentin in combination with SNRI venlafaxine was found to be more effective in improving symptoms of pain, fatigue, mood disturbance and insomnia in patients with neuropathic pain who did not respond to gabapentin monotherapy.[67] Combinations of TCA and SSRI have also been proven more effective than either medication used alone.[68]

Other SSRIs (fluoxetine, fluvoxamine, citalopram and paroxetine) and TCA (amitriptyline, desipramine) have all been studied for treatment of FMS but most showed modest efficacy at best. A 2009 meta-analysis of 18 randomised, placebo-controlled studies of a variety of anti-depressants showed strong evidence for efficacy of anti-depressants for pain relief, fatigue, depressed mood, sleep disturbance and in improving health-related quality of life.[69]

As there is no inflammation present in FMS patients, anti-inflammatory drugs such as NSAIDS and steroids, are not effective.[46] However, they have a role if there is concomitant inflammation condition which serves as a nociceptive trigger. Paracetamol helps pain relief but often insufficient when taken alone. Paracetamol in combination with tramadol, a narcotic that combines μ-opioid agonist-antagonist and SNRI activities may be helpful.[70] Common side effects of tramadol are nausea, constipation and pruritis. However, the risk of abused and dependence with tramadol is low as compared to other opioids.

Other pharmacologic modalities included use of human growth hormone, dehydroepiandrosterone (DHEA), 5-hydroxytryptophan, topisetron and pramipexole remain under investigation. Most of these drugs attempt to combat fatigue, rigidity, insomnia or poor sleep.

Non-pharmacological Treatment

Non-pharmacolgical treatment modalities, including aerobic exercises, physical therapy, cognitive behavioural therapy (CBT), massage and acupuncture can be helpful. Few of these approaches have been demonstrated to have clear-cut benefits in randomised controlled trials.

The role of aerobic exercise has been supported by systematic review.[71] It was postulated that aerobic exercises can stimulate endogenous analgesic systems,[72] increase time spent in deep sleep[73] and increase a sense of well-being and control. The challenge is to start and maintain FMS patients in a structured exercise programme and the key here is to encourage exercise according to fitness level. Low impact exercise may be tailored to individuals with musculoskeletal problems.

Adjunctive CBT will be indicated for patients with prominent psychosocial stressors, and/or difficulty coping, and/or difficulty functioning.[74] CBT has also been proven on meta-analysis to improve FMS.[75] CBT addresses the various aspect of the biopsychosocial model of FMS and can decrease depression and pain.[76] Patient education as a modality has been found to have therapeutic effect with patient undergoing education intervention having had significantly more improvement than controls[77] but improvements are short-term. Appropriate patient selection may improve efficacy. More research is needed to confirm the effectiveness and to determine the best match of treatment components to particular sets of FMS symptoms.

Other modalities include acupuncture, trigger point or tender point injections, EMG-biofeedback, chiropractic or massage. There is increased interest to develop more effective non-pharmacological treatment modalities in FMS as our ability to accurately measure effect of treatment has improved. The multifaceted nature of FM suggests that multimodal individualised treatment programmes may be necessary to achieve optimal outcomes in patients with this syndrome.

Conclusion

Management of fibromyalgia requires knowledge of its broad spectrum of symptomatology that goes beyond addressing simple complaint of pain.[78] While diagnostic criteria do exist, they were originally developed for research purposes and need further refinement as understanding of fibromyalgia has evolved. Although diagnosis can be difficult, new treatments, better understanding of the pathophysiology and greater involvement of different specialities can pave the way for improvement in the diagnosis of FMS. Often, a multidisciplinary healthcare setting is required to address the multidimensional nature of FMS. Outcome measures borrowed from clinical research in pain, rheumatology, neurology and psychiatry enable treatment response in specific symptoms domains. Managing FMS patients encompass an art of practising medicine as much as knowing its scientific basis.

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